

An epidemic of dystonic reactions in central Africa

In December, 2014, an outbreak of suspected meningitis was investigated in Ituri District, northeastern Democratic Republic of Congo (DRC). Ituri shares borders with Uganda and South Sudan, is well known for political instability, and houses a large displaced population with limited access to health care. Meningitis was suspected by health workers due to neck spasm, interpreted as neck stiffness. However, further investigations (see appendix for details) suggested that bacterial meningitis was not the cause of this outbreak. In the outbreak response that followed, participants provided verbal informed consent prior to interviews, lumbar puncture, and urine collection and the Government of DRC approved the outbreak investigation plan.

The epidemiological pattern of the outbreak (curve, age distribution, evolution) was atypical for meningitis, there were few clinical symptoms or signs of this disease (eg, fever or neck stiffness), and only four of 83 patients who underwent lumbar puncture had cerebrospinal fluid evidence of *Neisseria meningitidis*. Review of videos of patients by paediatric neurologists suggested facial-truncal dystonia, possibly secondary to drug administration.

Dystonic reactions were defined as the presence of at least one of the following symptoms: muscle spasm of the face, neck, or arm; oculogyric crises; and protrusion and retraction of the tongue.¹ Between December, 2014, and August, 2015, 1029 admissions to Médecins Sans Frontières or Ministry of Health centres met the case definitions of dystonia or suspected meningitis; 930 patients had at least one episode of dystonia. 448 (48.2%) were male, 311 (33.4%) were younger than 5 years, 265 (28.5%) were aged 5–15 years, and 354 (38.1%) were older

than 15 years. The median duration of admission was 3.7 days (range 1–10). 11 patients died, five of whom were younger than 5 years (see appendix for further details).

When the diagnosis of toxic dystonia, and not meningitis, was suspected, the strategy of investigation changed to a search for a toxic agent causing extrapyramidal reactions. The management of patients with dystonic reactions was modified, lumbar punctures were only performed for those with clear evidence of meningitis, use of empirical antibiotics was reduced, and biperiden was used to alleviate dystonia.¹

Toxicological analysis was performed on urine samples from nine patients with dystonia (February and March, 2015) and 39 medicines available in pharmacies or procured at a government health centre (March and June, 2015) at the Pharmacology-Toxicology Service, Hôpital Raymond Poincaré, Garches, France. Liquid chromatography coupled to diode array, tandem mass spectrometry, gas chromatography coupled to mass spectrometry, and Q-Exactive hybrid quadrupole-Orbitrap mass spectrometry were conducted on all urine and drug samples (appendix).

Haloperidol was detected in urine from all nine patients with dystonia (median urinary concentration 4 µg/L [range <1 to 49 µg/L]). Haloperidol was also detected in all of nine yellow tablets imprinted with the letters "AGOG" and labelled as diazepam (figure). The median haloperidol dose per tablet was 13.1 mg (range 9.5–19.9). 15 mg of haloperidol is 20–25 times the usual daily maximal recommended dose for a 5 kg child. No diazepam or other toxic substances were detected. No haloperidol was detected in the other 30 medicine samples, which all contained the appropriate active pharmaceutical ingredients. Six of the nine AGOG-marked tablets were obtained from patients with dystonia who had ingested them, and three tablets were



Figure: Falsified diazepam tablets containing haloperidol

The tablets are light yellow in colour, are scored across the centre on one side, and bear the letters "AGOG" on the other.

bought in a pharmacy or procured at a government health centre.

The evidence suggests that this large outbreak of dystonic reactions, in a remote area of central Africa, was caused by the consumption of tablets labelled as diazepam but which in fact contained undeclared haloperidol. No alternative explanation was found to explain the clinical features observed. It is most likely that these were falsified medicines, deliberately and fraudulently mislabelled. This case emphasises the importance of investigating atypical clinical presentations and the need for multidisciplinary approaches. Meningitis was a reasonable working diagnosis, in a remote community, by primary health-care workers unfamiliar with dystonia. Further investigations revealed that, in this area of DRC, patients frequently receive diazepam over the counter to treat a wide range of illnesses for which diazepam should not have been used according to rational prescribing.

Although dystonic reactions are rarely life-threatening, they often cause distress, panic, and shame for patients and their families. Local public perceptions of the outbreak were not linked to the consumption of medication, but rather to meningitis or "evil spells/spirits". Joint action led to the posting of an international WHO alert about the circulation of falsified diazepam in sub-Saharan Africa.² Two types of falsified diazepam have been identified to date. Both products have tablets that are embossed with the mark "AGOG": falsified diazepam sold in bottles marked "Centaur Solina



See Online for appendix

Diazepam" and falsified diazepam sold in bottles marked "AGOG Diazepam". After review of the distributors in Uganda and other countries in the region, the same medicines distributor based in Kampala was identified as selling both falsified Centaur and AGOG products. AGOG Pharma Ltd (Vasai, India) stated that it does not manufacture diazepam but that it supplies haloperidol in blisters labelled as "AGOHAL, Haloperidol tablet BP 10mg". Centaur Pharmaceuticals (Mumbai, India) confirmed that it manufactures diazepam but not haloperidol.

Incorrect active ingredients in falsified medicines or negligently made substandard medicines have led to much harm in past tragedies, such as bone marrow failure from pyrimethamine-contaminated isosorbide-5-mononitrate in Pakistan.³ Weak medicines regulatory systems, with inadequate penalties, corruption, and porous borders, render populations extremely vulnerable to toxic and sub-therapeutic medicines. Both innovative and generic medicines of all major therapeutic categories are affected and there is industrial-scale production of falsified versions of some of the most heavily used medicines.⁴ In a 2010 WHO review of the capacity of 26 national medicine regulatory authorities in Africa, 14 "lacked a quality monitoring programme altogether".⁵ There is a great need for national and international support for medicines regulatory authorities in economically poor countries, as vital organisations for improving public health. We argue that this outbreak of severe toxicity through falsified medicines should be a wake-up call for the global public health community to ensure that all patients, especially those in vulnerable communities, benefit from rational prescribing and access to good quality medicines.

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